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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/153,133	09/15/98	LEE D	04712/018002

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EXAMINER	
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ART UNIT	PAPER NUMBER
1619	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/153,133	LEE ET AL.	
	Examiner	Art Unit	
	Shahnam Sharareh	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3,5,6,8-31 and 33-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,5,6,8-31,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Continued Prosecution Application

1. The request filed on March 08, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/153133 is acceptable and a CPA has been established. An action on the CPA follows.

Status of the Claims

Claims 1-3, 5-6, 8-31, 33-44 are pending.

Priority

Priority of the instant application as set fort in Paper No. 6 is September 15, 1998.

Response to Arguments

2. Any rejection that is not addressed in this Office Action is considered obviated. Applicant's arguments with respect to the rejection of claims 1, 13-15, 38-44 under 112, first paragraph, has been fully considered and are found persuasive. Examiner views the recitation of the solid component to encompass dry precursors (page 52 line 2) comprising amorphous calcium phosphate.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 22, 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for adjuvant compositions comprising calcium phosphate, does not reasonably provide enablement for adjuvant compositions

comprising second adjuvant selected from the group polymers and methods of delivering such compositions wherein the second adjuvant is a polymer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Polymers encompass a plethora of compounds. Determining the toxicity and efficacy of all such compounds for *in vivo* use require undue experimentation. The specification does not provide guidance as to how one skilled in the art would go about selecting polymer of choice in forming the instant compositions. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compositions in eliciting an immune response. The state of art only provides for the natural polysaccharide adjuvants that are readily use to enhance therapeutic delivery (see Kossovosky et al), therefore, there is no predictability in the art with respect to the whole class of polymers. Further there are neither working examples nor teachings in the specification that enable one skilled in the art how to first identify the desired polymers, and second determine the desired ratio strength of incorporated ingredients, in order to practice the claimed invention. Therefore, the amount of guidance presented in the specification fails to present a required amount of guidance to perform the claimed invention without undue experimentation.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 12, 25, 28, 36-37, 38 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 37, the recitation "the first adjuvant" lacks antecedent basis.

In claims 28 37-38, it is not clear what is meant by the phrase "elicit a response of a specific immune cell type". This recitation is vague. It is not clear to which specific immune response or which specific immune cell type is applicant referring?

In claims 12, 25, 36 the recitation of "RANTES, Fas ligand, OSM, LIF, 4-1BBL, MCP-1, MIP are indefinite. Specification further fails to provide adequate teaching as to which cytokines are meant by the recited terms.

Claims 43-44 objected to under 37 CFR 1.75 as being a substantial duplicate of claim 23. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 43-44 do not further add any additional components to the composition of claim 23, instead they appear to recite a functional limitation that does not further limit the composition of claim 23.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15-16, 19-21, 23, 38, 39, 43-44 rejected under 35 U.S.C. 102(b) as being anticipated by Towey US Patent 2,967,802.

The instant claims are directed to compositions comprising at least a first adjuvant comprising calcium phosphate paste.

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater, 162 USPQ 541, 550 - 51 (CCPA 1969). In this case, Towey meets all the limitations of the instant claims. Towey discloses calcium phosphate compositions for delivery of antigens for use as a vaccine for *Erysipelotherix rhusiopathiae* (col 3, lines 54-56; col 4, lines 4-9, col 5, lines 24-37). Calcium phosphate composition of Towey is in the form of a gel (an amorphous and paste form). Towey's composition contain a secondary suspending agent such as Kaolin, pectin, or magnesium trisalicate that are capable of producing a response toward a specific agent, thus meeting the limitation of a second adjuvant. Since Towey's compositions meet all the limitations of the instant compositions, they are also inherently capable of performing their instant functional limitations.

6. Claims 15-16, 19-20, 23-25, 27, 38, 39, 43-44 rejected under 35 U.S.C. 102(b) as being anticipated by Relyveld US Patent 4,016,252.

Relyveld discloses calcium phosphate gel compositions in the form of a poliomyelitis or anti-rabies vaccine (example 1-2). Relyveld's composition is in an

injectable aqueous gel form and contains all the limitations of instant amorphous paste formulation (claims 1-10). Relyveld also discloses an increase immunogenecity when coadministerating an antigen with a suitable calcium phosphate gel as a vaccine formulation (abstract). The recitation of "capable of hardening at body temperature" does not further limit components of composition and is viewed as a functional limitation. Relyveld disclose all compositional limitations of the instant claims.Therefore, Relyveld meets the limitations of instant claims.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims claim 1-3, 5-6, 8, 10-14, 17-18, 23-27, 39, 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyveld US Patent 4, 016,252, in view of Amerongen et al US Patent 5,443,832, and Constantz et al US Patent 5,782,971.

The instant claims are directed to adjuvant compositions comprising amorphous calcium phosphate, and methods of using thereof.

Relyveld teaches methods of improving vaccine formulations by using calcium phosphate gels (an amorphous formulation) as an adjuvant wherein the calcium to phosphate ratio is from 1.62 to 1.85 (col 2 lines 1-15). Reyveld fails to show the instant 40 wt % solids in his compositions.

Amerongen is used to show that calcium phosphate particles (hydroxy appetite) is used in amounts of higher than 40% to elicit an immune response in mammals. Amerongen teaches 1mg of HA in 200 μl of PBS (example 2). Amerongen fails to teach their compositions in an injectable paste form.

Constantz et al teach amorphous calcium phosphate containing compositions as a suitable drug delivery vehicle (col 2, lines 60-67; col 6, lines 61-63). Constantz specifically teach paste formulations of calcium phosphate that are capable of hardening after administration (col 6, lines 40-50). Constantz's composition comprise about 15 wt% of the dry ingredient (solid component) having particle sizes of about o.5-500 microns (col 5 lines 1-3; and lines 14-25). Constantz further indicates that one of ordinary skill in the art would be able to modify the viscosity of his composition by varying the percentages of solids in his composition, thus allowing for ease of

administration (col 6, lines 32-39). Constantz, however, fails to disclose vaccine formulations.

All cited art teach various methods of using calcium phosphate particles suitable in drug delivery systems, therefore, their teachings are viewed to be analogous.

It has been established that the prior art can be modified or combined to reject claims as prima facia obvious as long as there is a reasonable expectation of success. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to modify concentrations of Relyveld calcium phosphate adjuvant composition to contain about 40 wt % solid component, as shown by Amerongen, and further adjust the viscosity of the composition, as taught by Constantz, by modifying the percentages of the solid component (the calcium phosphate component) and formulate a hardenable calcium phosphate formulation that is easily administered to the site to be treated.

8. Claims 9, 22, 28-31, 33, 34-38, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Relyveld US Patent 4, 016,252, in view of Amerongen et al US Patent 5,443,832 and Constantz et al US Patent 5,782,971, as applied to claim 1-3, 5-6, 8, 10-14, 17-18, 23-27, 39, 43-44 above, and further in view of and Gupta et al (Vaccine Design, Chapter 8 pp 229-248, 1995), or Kossovsky et al US Patent 5,462,751.

The instant claims are directed to adjuvant compositions comprising calcium phosphate and a second adjuvant.

The teachings of Relyveld, Amerongen and Constantz are discussed above.

Gupta also teaches calcium phosphate compositions that can be used as adjuvant in vaccine (see page 239, 241 sec 3.2). Gupta specifically teaches that the quality of calcium phosphate products depends on the concentration of reactants, and the rate at which the reactants are mixed (page 240). Finally, Gupta teaches that the potency of vaccine formulations can be increased by incorporation of other adjuvant-active components (page 241, last paragraph). However, Gupta does not specifically teach various percentages of solid amount, or the use of a cytokine as a secondary adjuvants.

Kossovsky et al teach compositions comprising calcium phosphate (brushite) compositions that are suitable for delivery in immune response eliciting moieties such as peptides and proteins (abstract, example 1-2). Kossovsky further teaches attaching a biologically active peptide or protein to his calcium phosphate compositions for delivery of such immunostimulatory complexes (examples 3-5). The brushite particles of Kossovsky are less than 1000 nm, more specifically 5 nm to 150nm (col 3, lines 62-65; col 6, lines 52-55). Kossovsky states that because of its small particles their nanoparticles can avoid being removed from circulation by RES, thus providing motivation to the size properties of his drug delivery systems. Peptides used in Kossovsky's compositions can be selected from any immunologically pair members such as IgG, IgM etc..polycolonal or monoclonals specific to a cell surface antigen (col 5, lines 65-67;col 6, lines 1-10). Kossovsky also teaches coating of his core complex by using a second type component such as Cellobiose (a natural polymer) to enhance

specificity of his formulations (abstract, example 2). Kossovsky, however, fails to specifically teach a hardenable paste formulation for injection.

Nevertheless, it would have been obvious to one of ordinary skill in the art at the time of invention to modify concentrations of Relyveld calcium phosphate adjuvant composition to contain about 40 wt % solid component, as shown by Amerongen, and further adjust the viscosity of the composition, as taught by Constantz, by modifying the percentages of the solid component (the calcium phosphate component) and formulate a hardenable calcium phosphate formulation that is easily administered to the site to be treated. Furthermore, one of ordinary skill in the art would have been motivated to incorporate a second adjuvant, separately, as taught by Gupta; or in the form of a coating, as taught by Kossovsky, to enhance the potency and the therapeutic efficacy of Relyveld's vaccine.

Conclusion

9. No claims are allowed. Examiner requests a copy of all pending claims along with the Applicant's response to this Office Action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Diana Dudash can be reached on 703-308-2328. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

ss
May 20, 2001

DIANA DUDASH
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